and as stressed throughout the specification, (see page 6 for example) the hybrid cytokine of the invention constituted of the bioactive form of IL-7 and HGFβ selectively supports the proliferation and subsequent differentiation of pre-pro-B cells. At page 6, 2nd full paragraph the inventors state:

"Although IL-7 plays an essential role in the development of early B lymphocytes, IL-7 alone doesn't support the proliferation of pre-pro-B cells. Although HGF can synergize with IL-3, GM-CSF or erythropoietin to support the growth of HPCs, myeloid cell lines, and erythroid cells, respectively, it has not been reported to play a direct role in the early B-cell development. Hence, the discovery of the IL-7/ HGFβ complex not only provides a reagent that regulates the earliest stages of B-lymphocyte development in bone marrow, but it may presage the existence of a series of other naturally occurring hybrid cytokines as well as the artificial creation of hybrid cytokines with unique pharmacological properties. In addition, the existence/creation of hybrid cytokines may render pleiotropic growth factors lineage-specific, thereby directing the commitment of hemopoietic and other pluripotent stem cells to development along selective pathways."

Claims 1-27 all of the claims under consideration have been cancelled and new claims 32-52 substituted therefor.

As amended, the rejection of original claims 11 and 17 under 35 U.S.C. § 112, second paragraph has been mooted. As to the rejections under 35 U.S.C. §

112, certain of the claims have been amended so as to obviate the specific rejections and in other instances, the applicants' position as to why the rejections are not justified have been presented.

The Examiner contends that claims 1-27 contain subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors had possession of the claimed invention at the time the application was filed. The disclosure must convey intelligence to one capable of understanding, the person of ordinary skill in the art, here a person of very high skill (it is noted that even the Examiner has a Ph. D.) and not the general public. N.L. Gore and Assoc. v. Garlock, Inc., 721 F.2d 1540, Md U.S.P.Q. 303 (Fed. Civ. 1983). The skilled in the art would be familiar with the starting materials i.e., hepatocyte growth factor (HGF) and furthermore the applicants provide a great deal of information about HGF (see pages 1-3, for example). The same is time of the starting material IL-7 (see pages 3-5, for example). The invention herein is of the IL-7HGFβ complex. The applicants have described how the complex is produced (see for example p. 14, first full paragraph, pages 3-4, etc.) The applicants have also described to the skilled in the art the bioactive protein product which includes the bioactive portions of IL-7 and HGFβ connected with a flexible linker and how this product is produced. Examples of linkers are detailed (p.7, 2nd paragraph) so that the skilled in the art would encounter no problem in practising this aspect of the

invention, no undue experimentation would be required for preparing and using the IL-7/HGFβ complex with or without the flexible linker. It is pointed out, in this regard, that while no undue experimentation is required, that some experimentation is necessary does not preclude enablement. DeGeorge v. Bernier, 768 F.2d 1318, 226 U.S.P.Q. 578 (Fed. Cir. 1985). Some trial and error is of course permissible. W. L. Gore and Assoc. v. Garlock, Inc. 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983). Indeed it may be sufficient if enablement of use is obvious from the prior art. Cross v. Iizuka, 753 F. 2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985).

The rejection of claims 1-22 with respect to the sequence identities has been avoided as this language no longer appears in the claims.

The terms "biologically active variant" also has been limited to those variants expressly disclosed in the specification, (see for example the first full paragraph at page 8 of the specification).

The instant starting materials, their properties, their preparation, etc. are well known and there is a great deal of literature, including that which has been contributed by the inventors named herein. The skilled in the art are aware of this literature and can rely on it if any question vis-à-vis production, identity, and the like arise. A particular example of this is the article appearing in the Journal of Immunology, 2001, 167:3550-3554 authored by the inventors and directed to this same subject matter. While this article carries a date subsequent to the

application's filing date, it sets forth numerous citations expressly addressing the issues raised by the Examiner. It is important in this regard to consider p. 3557 where identification, and sequencing are set forth and where the β-chain of HGF is identified and where in Figure 1, the following appears the "comparison with the predicted amino acid sequences for the HGFβ-chain in mouse, rat and human as derived from the published nucleotide sequences . . . (emphasis ours)" A copy of this article is enclosed. The references relied on by the author, for example items 3, 4, and 5 in the article are indicative of the art which was available at the time of the filing of this application.

The rejection of the claims with respect to the use of the "linker" which is disclosed and exemplified at page 7 has been limited to low molecular weight oligosaccharides.

As to providing disclosure for guiding the skilled in the art "how to generate a IL-7 and the β-chain of HGF other than that exemplified in the specification," this is more than adequate as these are known materials, well documented in the literature (see our remarks above) and particularly the availabiity of extensive literature as to those materials.

As to the rejection of the claims with respect to application of the hybrid cytokine, the specification states that "PPBSF has been found to selectively stimulate the proliferation of pre-pro-B cells and to support the generation of pro-B cells (the next recognized stage in early B-lymphocyte development). PPBSF

"primes" pre-pro-B cells to proliferate in response to monomeric IL-7 in an anchorage-independent fashion by upregulating the expression of the IL-7 receptor (R) α chain. PPBSF also upregulates the expression of terminal deoxynucleotidyl transferase (TdT) and initiates the expression of cytoplasmic immunoglobulin mμ heavy chain (cμ). PPBSF also stimulates the proliferation of thymocytes. This is the first demonstration of a naturally occurring, or an artificially constructed, hybrid cytokine (i.e. a biomolecular or unimolecular complex of the bioactive portions of two or more disparate cytokines or growth factors). It also is the first demonstration of a bioactive form of IL-7 and HGFβ that selectively supports the proliferation and subsequent differentiation of pre-pro-B cells. Although IL-7 plays an essential role in the development of early B lymphocytes, IL-7 alone doesn't support the proliferation of pre-pro-B cells. Although HGF can synergize with IL-3, GM-CSF or erythropoietin to support the growth of HPCs, myeloid cell lines, and erythroid cells, respectively, it has not been reported to play a direct role in the early B-cell development. Hence, the discovery of the IL-7/ HGFβ complex not only provides a reagent that regulates the earliest stages of B-lymphocyte development in bone marrow, but it may presage the existence of a series of other naturally occurring hybrid cytokines as well as the artificial creation of hybrid cytokines with unique pharmacological properties. In addition, the existence/creation of hybrid cytokines may render pleiotropic growth factors lineage-specific, thereby directing the commitment of

hemopoietic and other pluripotent stem cells to development along selective pathways."

At pages 18-20, the wide ranging applications of the PPBSF of the invention are set forth in detail. At page 20, in particular it is noted that "inasmuch as PPBSF also stimulates proliferation of immature thymocytes, it may prove to be equally useful in treating disorders of T lymphocytes as well as B lymphocytes. Indeed, should PPBSF induce commitment of HSC to bipotential lymphoid differentiation, it could be used to correct severe combined immunodeficiency disorders, possibly including AIDS."

There is no requirement that the applicants establish the effectiveness of the hybrid cytokine in treating AIDS in humans. The applicants have established by in vitro experiments the ability of PPBSF to generate pre-pro-β cells in vitro and its application to immunodeficiency. (Page 20 of the application). the skilled in the art would be able to formuate these preparations and to administer them as is conventional in the art. The Examiner's coments that "there cannot be said to be any reasonable expectation of success at the in vivo application of a potential therapy with the hybrid cytokine . . ." is not supprted other than by the Exainer's assertion of this. In contrast, the literature (see the enclosed article, p. 3553, col 1, first full paragraph, which states that "HGF increases the generation of mature T cells . . ."

The Examiner has cited WO95/13393 in this case. The applicants herein wish to incorporate by reference there to, pages 14-15 of that published application. The portions relied on expressly provide that "the properties of a particular hybrid can be ascertained through standard in vitro tests known in the art" Page 15, details the therapeutic application of hybrid cytokines. It should be noted that the applicants carried out not only in vitro studies but animal studies for determining usefulness of the hybrid cytokines (page 19 of the specification).

For all of the reasons set forth above, the Examiner's rejection of the claims on disclosure and enablement is not well taken and should be withdrawn.

Claims 5, 9-11 have been rejected under 35 U.S.C. 103(a) as being impatentable over WO 95/133393, Claim 5 has also been rejected as anticipated by the same reference.

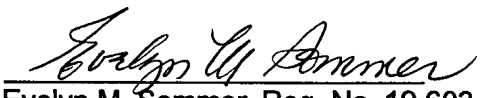
The hybrid cytokines disclosed in the reference are very different from those claimed herein. They specifically comprise: 1) three or four α-helical sequences, the α-helical sequences selected from cytokine α-helical sequences, the cytokine being selected from the group consisting of leukemia inhibitory factor (LIF), granulocyte colony stimulating factor (G-CSF), interleikin-6 (IL-6), interleukin-11 (IL-11), ciliary neurotrophic factor (CNTF), and oncostatin-M (OSM); and 2) at least three linking sequences, the linking sequences selected from at least a portion of a linking sequence from any of the foregoing cytokines,

wherein at last of the three or four α-helical sequences is derived from a different cytokine than at least one other of the three or four α-helical sequences.

The hybrid cytokines of the invention firstly involve IL-7 which is not mentioned or suggested by the reference. Instead IL-76 and IL-11 are utilized. Secondly, the hybrid cytokine of the invention is IL-7/HGFβ and possibly the bioactive portions of IL-7 and HGFβ connected with a flexible linker. The very much detailed description of the reference makes it clear that it is only IL-6 and IL-11 are there involved. There is nothing in this reference that would suggest the hybrid cytokines of the invention containing as a critical ingredient IL-7.

The Examiner is respectfully requested to reconsider the application with a view to allowance of all of the claims.

Respectfully submitted,

By: 

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